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WO 2004/005544 A3

(54) Title: MARKER GENES FOR DETERMINING RENAL TOXICITY

(57) Abstract: Methods are disclosed for fast and accurate readout of kidney toxicity before it occurs and before it is demonstrated by histopathology examination. Ultimately this approach shall allow earlier compound selection. The twelve genes identified, namely Calbindin-D28k, KIM-1, OPN, EGF, Clusterin, VEGF, OAT-K1, Aldolase A, Aldolase B, Podocin, Alpha-2u and C4, were grouped and ultimately can be assessed in the form of a kit using PCR, a high throughput technology, in order to characterize and rank new compounds according to their anticipated general kidney toxicity. Also disclosed are methods for identifying agents useful in the treatment of kidney disease, methods for monitoring the efficacy of a treatment for kidney disease and kidney-specific vectors including the sequences of the disclosed genes, and a method for identifying a candidate gene associated with a biological process including kidney function.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/06537 A (GREEN CYNDI D ;RAHA DEBASISH (US); BIOGEN INC (US); CATES RICHARD) 24 January 2002 (2002-01-24) page 55, line 28 - page 59 claims 1-41	1-12, 19-60
X	WO 02/10453 A (PORTER MARK W ;CASTLE ARTHUR L (US); GENE LOGIC INC (US); JOHNSON) 7 February 2002 (2002-02-07) claim 1; tables 1-3	1-12, 19-60

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2003	13. 02. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gabriels, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07111

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AICHER LOTHAR ET AL: "New insights into cyclosporine A nephrotoxicity by proteome analysis" ELECTROPHORESIS, vol. 19, no. 11, August 1998 (1998-08), pages 1998-2003, XP008024561 ISSN: 0173-0835 the whole document	1-12, 19-60
A	WO 99/37757 A (INST NAT SANTE RECH MED ;VERROUST PIERRE J (FR); HAMMOND TIMOTHY G) 29 July 1999 (1999-07-29) claim 20	1-12, 19-60
A	WO 02/06529 A (PHAKDEEKITCHAROEN BUNYONG ;GERMINO GREGORY G (US); WATNICK TERRY J) 24 January 2002 (2002-01-24) claim 25	40-42
A	US 2002/037508 A1 (LANDER ERIC S ET AL) 28 March 2002 (2002-03-28) page 22; table 1	40,42
A	US 2001/034023 A1 (STANTON VINCENT P ET AL) 25 October 2001 (2001-10-25) claim 1	40,42
P,X	WO 02/066682 A (FARR SPENCER B ;FARRIS GEORGIA (US); HICKEN SAMUEL H (US); PHASE 1) 29 August 2002 (2002-08-29) the whole document	1-12, 19-60

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07111

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-18
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 5-9, 11, 12, 19, 20, 23, 24, 26-28, 31, 32, 34-37, 39, 40
42-53 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-12 are directed to a diagnostic method practised on the human/animal body (these claims contain the step of obtaining a sample from an individual), the search has been carried out and based on the correlation between the expression level of a selected gene and renal toxicity.

Although claim 19-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the embodiment of claim 35.

Continuation of Box I.1

Claims Nos.: 13-18

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1, 2, 5-9, ,11, 12, 19, 20, 23, 24, 26-28, 31, 32, 34- 37, 39, 40, 42-53 (all partially)

1.1. claims: 1, 2, 5-9, ,11, 12, 19, 20, 23, 24, 26-28, 31, 32, 34-37, 39, 43-53 (all partially)

Methods using the correlation between the expression level of Calbindin-D28k and renal toxicity for diagnosis and drug screening and kits therefore.

1.2. claims: 40, 42 (both partially)

The use of a polymorphism in the Calbindin-D28k gene for the diagnosis of renal toxicity.

Invention 2: claims 54-60 (all partially)

Methods for identifying candidate genes associated with biological processes including kidney function, renal toxicity, and/or kidney disorders by comparing the expression level of Calbindin-D28k with the expression level of candidate genes.

Invention 3: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in KIM-1 and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 4: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in OPN and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 5: claims 1-12, 19-60 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods using the correlation between the expression level of/or polymorphisms in EGF and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 6: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Clusterin and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 7: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Alpha-2u globulin related-protein (Alpha-2u) and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 8: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Complement component 4 (C4) and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 9: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Vascular Endothelial Growth Factor (VEGF) and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 10: claims 1-12, 19-60 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods using the correlation between the expression level of/or polymorphisms in Kidney-specific Organic Anion Transporter-K1 (OAT-K1) and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 11: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Aldolase A and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 12: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Aldolase B and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

Invention 13: claims 1-12, 19-60 (all partially)

Methods using the correlation between the expression level of/or polymorphisms in Podocin and renal toxicity for diagnosis, for gene identification, and for drug screening and kits therefore.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/07111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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